R E M A R K S

Request for Correction of Printing
Errors in the Published Application

It is respectfully requested that the following printing errors in the published application (US 2006/0040030A1) of the above-identified application be corrected:

page 3, line 23 of paragraph [0026], replace "phosphate" with --phosphite--;

page 4, line 10 of paragraph [0029], replace "phosphate" with --phosphite--;

page 6, claim 4, last line, replace "phosphate" with --phosphite--.

The above three occurrences of the term "phosphite" appear in the applicants' originally filed English-language translation (filed June 1, 2005).

The aforesaid printing error in claim 4 was previously pointed out by applicants' counsel on page 2, second paragraph in an AMENDMENT filed June 10, 2008.

Amendment to the Specification

Table 6 on page 20 of the specification was amended to correct a clerical error in the reporting of a value in the table. The undersigned was informed of this clerical error by the applicants.

Claim Amendments and New Claims

Claims 1, 16 and 31 were amended to better define applicants' invention. The term "plant pathogenic fungi of cereals" recited in amended claims 1, 16 and 31 is supported on page 1, line 8 of the specification. Also, editorial revisions were made to claims 1 to 34.

New claim 35 includes the features of claims 29, 30 and 31 and a feature supported in the specification on page 5, lines 14 to 15 (deoxynivalenol ("DON") being reduced to 1.1 ppm or less).

Claim Objection

Claim 30 was objected to under 37 CFR 1.75(c) for the reason set forth at the top of page 3 of the Office Action).

Claim 30 was amended to avoid the claim objection.

Withdrawal of the objection to claim 30 is respectfully requested.

Discussion of the Presently Claimed Invention in the Context of the Art

The presently claimed invention is directed to reducing mycotoxin contamination in a cereal comprising applying to the cereal an amount of at least one compound effective for inhibiting production of mycotoxin by plant pathogenic fungi of cereals, wherein the compound is selected from the group consisting of an ammonium salt, a primary to quaternary ammonium salt, an alkali metal salt, an alkaline earth metal salt and a polyvalent metal salt of phosphorous acid or a phosphite ester.

It has heretofore been known that Fusarium head blight is a disease which results in great damage to cereals. Fusarium head blight is caused by fungi.

The plant pathogenic fungi which cause this Fusarium head blight produce more than one toxic metabolite referred to as mycotoxin, which contaminates crops during cultivating and poses a risk of ingestion by human and domestic animals through migration to harvestries and processed foods.

Mycotoxins are produced by molds that form in grains, food and feedstuffs and, thus, can cause health concerns when ingested. The occurrence of mycotoxins in foods is usually the result of mold contaminated grain at pre-harvest or during storage. Fusarium and Alternaria molds attack the plant in the field prior to harvest of grain or fruit; Aspergillus or Penicillium molds affect grains under storage conditions conducive to mold growth. These molds often produce the toxins deoxynivalenol (DON), alternariol, aflatoxin, and ochratoxin A.

Deoxynivalenol (DON) (often referred to as vomitoxin) is a naturally occurring mycotoxin produced by several species of Fusarium fungi. Specific modes of action have been identified in swine that explain this toxin as the primary cause of feed refusals, diarrhea, vomiting, reproductive failures, and death. DON in cattle has been associated with reduced feed intake and

lower milk production. It is considered that DON may be a marker for the presence of other mycotoxins in problem feeds.

Vomitoxin (DON) causes reduced animal feeding and weight gain (especially swine) at levels as low as 1 to 3 ppm. In the field, DON has been associated with reduced performance in dairy cattle at 1.5 to 2.5 ppm in the ration. It is believed that DON serves as an indicator for spoilage and the probable presence of unidentified factors more toxic than DON itself.

The FDA recommended maximum concentration of DON in ruminating cattle is 5 ppm in a total ration and 10 ppm in grain, not to exceed 50% of the diet.

DON is thus a serious problem in that DON causes acute poisoning, which results in emesis (vomiting) and diarrhea in animals. DON also causes vomiting in humans.

An industry standard for a safe amount of DON in finished wheat products for human consumption has been established as 1.1 ppm or less.

In addition to the health problems, mycotoxins cause serious economic hardship. It has been estimated that mycotoxins can cause annual losses in grain commodities in the United States of

over one billion dollars. Guidelines and recommendations for mycotoxins in both animal feed and food destined for human consumption make the sale of contaminated grain in the United States very limited.

The control of Fusarium head blight by application of fungicides does not, however, necessarily sufficiently reduce DON contamination.

Heretofore, it has long been desired to develop a method for substantially reducing DON contamination of cereals. The presently claimed invention satisfies this need.

Obviousness Rejection Under 35 USC 103

Claims 11 to 13, 15 to 18, 20 to 25, 27 to 29 and 31 to 34 were rejected under 35 USC 103 as being unpatentable over Staub et al. (USP 4,849,219) in view of Pirgozliev et al., European Journal of Plant Pathology, (2002), 108:469-478 for the reasons set forth on pages 4 to 7 of the Office Action

It was admitted in the Office Action that Staub et al. do not teach reducing mycotoxin, wherein the mycotoxin is deoxynivalenol. More to the point, Staub et al. do not mention mycotoxin, let alone deoxynivalenol.

Staub et al. concern microbicides. In the paragraph bridging columns 3 and 4, Staub et al. describe over twenty-five different fungicides. There is no teaching or suggestion in Staub et al. to pick two of the fungicides referred to in the Office Action out of such twenty-five different fungicides disclosed by Staub et al.

Staub et al. list almost seventy different species of plants in column 5. There is no teaching or suggestion in Staub et al. to select wheat out of such seventy different plant species.

Staub et al. list fifteen different fungi at the top of column 5, without any direction to choose fusarium from this list. Moreover, only selected species of fusarium produce DON.

Due to the aforementioned deficiencies in Staub et al., the Pirgozliev et al. reference was applied.

Pirgozliev et al. concern only a study wherein metconazole and azoystrobin, fungicides used for the control of Fusarium head blight, resulted in elevated concentration of deoxynivalenol (DON).

Pirgozliev et al. do not teach or suggest any of the compounds effective for inhibiting production of mycotoxin by plant pathogenic fungi of cereals which are recited in applicants' claims.

Pirgozliev et al. do not teach or suggest reducing DON to a safe level, such as 1.1 ppm or less (see applicants' claim 35).

As disclosed at the middle of page 4 of applicants' specification, it has been demonstrated that not all of the pathogenic fungi which cause Fusarium head blight produce DON contaminations. Accordingly, based on the knowledge involving Fusarium head blight, it is respectfully submitted that one of ordinary skill in the art would not know precisely what fungicide to apply to reduce DON to an acceptable safe level.

The presently claimed invention selectively reduces DON to a level approved by the FDA, regardless of the presence or absence or the degree of Fusarium head blight of cereals.

As discussed in the paragraph bridging pages 4 and 5 of the present specification, even when the Fusarium head blight of the cereals is controlled by combined application of various fungicidal agents, DON is frequently detected at more than 1.1 ppm.

In view of the above, it is respectfully submitted that one of ordinary skill in the art would not consider combining the references in an attempt to arrive at applicants' presently claimed invention. Even assuming *arguendo* that the references were combinable, it is respectfully submitted that such combination would lead one of ordinary skill in the art to the

presently claimed invention.

Clearly, the presently claimed invention is not based on the fungicidal effects of various fungicides or the control or lack thereof of Fusarium head blight. This is clear from the data set forth in the specification, which is discussed hereinbelow.

A. Table 1 on page 10 of the specification is reproduced as follows:

Table 1. Inhibitory effect of phosphite derivative and alkyl phosphite derivative on DON concentration

Test No.	Treatment			DON concentration (ppm)	Incidence rate of Fusarium head blight for panicles (%)
	Active ingredient	Concentration	Control system		
1	Potassium phosphite	0.038%	Conventional control	2.41	0.3
2		0.070%	Conventional control	0.59	0.0
3		0.112%	Conventional control	0.39	0.9
4			No control	0.69	1.2
5	Fosetyl	0.120%	Conventional control	0.84	0.0
6	Potassium phosphate	0.112%	Conventional control	4.66	0.0
7			Conventional control	6.16	0.9
8			No control	8.69	4.9

Note) The concentration of the active ingredient A is the concentration converted into P_2O_5.

Note) The incidence rate of Fusarium head blight for panicles was calculated by counting the number of panicles in 1 m^2 of each section and the number of diseased panicles included therein.

The above Table 1 shows that DON was detected at highly contaminated levels, which were much higher than the safe standard value of 1.1 ppm, with no control and with a conventional control alone using a fungicidal composition for controlling of Fusarium head blight of cereals. On the other hand, inhibition of DON contamination depending on treated concentrations was observed with the use of potassium phosphite and the aluminum salt (generic name: fosetyl) of tris(ethylphosphonate) (according to the presently claimed invention), and their contamination levels were lower than 1.1 ppm.

It is worthy of special mention that even without any control where a conventional control was not performed, the DON contamination concentration was sufficiently reduced by applying potassium phosphite (according to the presently claimed

invention). Furthermore, even when potassium phosphate, which is a salt of normal phosphoric acid, was applied, the DON inhibitory effect was low, and thus it is clear that the phosphite and alkyl phosphite derivatives play an important role. Even when the incidence rate of Fusarium head blight for panicles was at almost the same degree, DON at a high concentration was detected when potassium phosphite was not applied.

It is thus evident that the concentration of DON contamination was reduced by the treatment with phosphorous acid and alkyl phosphorous acid and derivatives thereof, according to the presently claimed invention.

Potassium phosphite alone (0.112%: Test 4): The occurrence of Fusarium head blight was lower than without a control (Test 8), but the inhibitory effect thereof was lower than of the conventional control (Test 7). On the other hand, with regard to the DON concentration, it was markedly lower than that of the conventional control test (Test 7). Moreover, when the potassium phosphite was applied in combination with a conventional control (0.112%: Test 3), not only the occurrence of Fusarium head blight, but also the DON concentration was controlled.

Conventional control alone (Test 7): The occurrence of Fusarium head blight was lower than that of the no control test (Test 8), but the DON concentration thereof was slightly lower than that of the same. This shows that the occurrence of Fusarium head blight was reduced by a fungicide, but the control of DON contamination was not achieved.

B. Test 2 on page 12 of the specification is reproduced as follows:

Table 2: DON contamination concentration of grains diseased with Fusarium head blight

Test No.	Treatment			DON concentration (ppm)	
	Active ingredient A	Concen-tration	Control system	healthy grain	diseased grain
1	Potassium phosphite	0.038%	Conventional control	0.05	76.6
2		0.070%	Conventional control	0.04	44.7
3		0.112%	Conventional control	0.04	25.4
4			No control	0.04	75.6
5	Fosetyl	0.120%	Conventional control	0.96	11.0
6	Potassium phosphate	0.112%	Conventional control	0.06	86.9
7			Conventional control	1.72	90.0
8			No control	0.73	173.0

Note) The concentration of the active ingredient is the concentration converted into P_2O_5.

Note) The grains colored with scarlet or orange inherent for Fusarium head blight and shrink grains were sorted as the diseased grain, and the grains other than those were sorted as healthy grains.

The concentration of DON contamination of the healthy grains varied almost within a lower range. On the other hand, in the diseased grains with Fusarium head blight, DON was detected at an extremely high concentration as expected. However, in the crude wheat determined to be the diseased grains, a difference was observed in the concentration of DON contamination. That is, in the treatment with potassium phosphite (according to the presently claimed invention), the DON contamination concentration decreased depending on the concentration of potassium phosphite. It is thus clear that applying potassium phosphite reduces the DON contamination in the wheat, regardless of the presence or absence or the degree of the Fusarium head blight disease.

Potassium Phosphite Tests 1 to 4: As compared with the DON concentration of the healthy grains in the Fosetyl-treated test (Test 5), the Conventional control test (Test 7) and the no

control test (Test 8), the DON concentrations of the potassium phosphite-treated tests (Tests 1 to 4) were lower.

Conventional Control Alone (Test 7): The DON concentration of 1.72 ppm in the healthy grains of this test is a concentration above the currently accepted standard. Such a DON contamination of healthy grains increases the possibility of migration of DON contaminated grains in the healthy grains, and it also has the possibility or risk that damage by DON contamination cannot be controlled only by prevention using a particular fungicide.

Table 5 on page 19 of the specification is reproduced as follows.

C. Table 5. Change over time of fungal growth and DON production in wheat treated with potassium phosphite

Treatment	Analysis item	Days of culturing			
		7 days	14 days	21 days	28 days
Potassium phosphite 5.6%	DON (ppm)	ND.	ND.	ND.	ND.
	Ergosterol peak area value	17952	115921	372377	350972
Non-treatment	DON (ppm)	6.3	4.43	4.29	37.8
	Ergosterol peak area value	150453	271882	367236	559014

Note) ND means that the analytical value is less than the detection limit (0.222 ppm) of the ELISA analysis kit.

The amount of ergosterol which is an indicator that the amount of fungi was continuously increased during the culture in the non-treatment, whereas a plateau was reached on the 21st day in the treatment with potassium phosphite. With respect to the amount of DON production, in the non-treatment test, the DON production was initiated at an early phase of the culture and substantially increased on the 28th day. In contrast thereto, in the treatment with potassium phosphite (according to the presently claimed invention), DON was not detected during the entire period of the culture. It is clear that application of potassium phosphite has a high inhibitory effect on the DON production, regardless of the presence or absence or the proliferation degree of the fungi for Fusarium head blight of cereals.

After 21 Days of Culturing: With regard to a number of fungi, they were substantially the same in the potassium phosphite-treated test and the non-treatment test, but there was a clear difference in the DON concentration between these tests (in

the potassium phosphite-treated test (according to the presently claimed invention), it was ND (not detected), whereas in the non-treatment test, it was 4.29 ppm).

After 28 days of Culturing: No change in the Ergosterol amount was seen in the potassium phosphite-treated test (according to the presently claimed invention), and the growth or proliferation of the fungi appeared to be stopped (as discussed above, "a plateau was reached on the 21st day)). After 28 days of cultivation, no DON was detected in the potassium phosphite-treated test (according to the presently claimed invention), so that the controlling effect of producing DON by potassium phosphite (according to the presently claimed invention) was clearly demonstrated.

D. Table 6 on page 20 of the present specification is reproduced hereinbelow:

Table 6. Effects of potassium phosphite concentration on fungal amount of Fusarium head blight pathogenic fungus of the cereals and the amount of DON production

Treatment concentration	DON (ppm)	Ergosterol peak area
0.056%	1.60	1834861
0.112%	0.41	1769582
0.28%	ND.	1810454
0.560%	ND.	1921693
2.800%	ND.	85891
Non-treatment	46.1	3601748

Note) ND means that the analytical value is less than the detection limit (0.222 ppm) of the ELISA analysis kit.

Considering the amount of ergosterol as an indicator of the amount of fungi, a substantial inhibitory effect on the fungicidal amount was observed with a water solution containing 2.800% potassium phosphite (according to the presently claimed invention). In the range of concentrations from 0.056 to 2.800% of potassium phosphite (according to the presently claimed invention) in the water solutions, the amount of DON was significantly lower than that in the non-treatment tests. It is thus clear that the application of potassium phosphite (according to the presently claimed invention) has a high inhibitory effect on the DON production, regardless of the presence or absence or the proliferation degree of fungi for the Fusarium head blight of cereals.

When the aim is to lower the DON concentration, there is no relationship between the lowering of the ergosterol peak area (i.e., the amount of fungi) and the lowering of the DON value.

Withdrawal of the 35 USC 103 rejection is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

Enclosed is a Form PTO-2038 in the amount of $52 in payment of one additional claim.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Enclosure: Form PTO-2038 in the amount of $52